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EXAMINER
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UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE PATENT TRIAL AND APPEAL BOARD

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*Ex parte* LARS DYRSKJØT ANDERSEN and  
TORBEN FALCK ORNTOFT

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Appeal 2014-003417  
Application 13/352,393  
Technology Center 1600

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Before JEFFREY N. FREDMAN, CHRISTOPHER G. PAULRAJ, and  
JOHN E. SCHNEIDER, *Administrative Patent Judges*.

FREDMAN, *Administrative Patent Judge*.

DECISION ON APPEAL

This is an appeal<sup>1</sup> under 35 U.S.C. § 134 involving claims to methods of using quantitative PCR to predict the likelihood of an individual's bladder cancer progression. The Examiner rejected the claims as indefinite, as failing to comply with the enablement requirement, as directed to non-statutory subject matter, and as anticipated. We have jurisdiction under 35 U.S.C. § 6(b). We affirm.

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<sup>1</sup> Appellants identify the Real Parties in Interest as Catalyst Assets LLC and Aros Applied Biotechnology A/S (*see* App. Br. 3).

*Statement of the Case*

*Background*

“[U]rinary bladder cancer is the fourth most common malignancy in males . . . . The disease basically takes two different courses: one where patients have multiple recurrences of superficial tumors (Ta and T1), and one which progresses to a muscle invasive form (T2+) which can lead to metastasis” (Spec. 1). “[I]t is often difficult to differentiate Ta from T1 stage tumors, and the two stages are often confused. The ability to predict which tumors are likely to recur or progress would have great impact on the clinical management of patients with superficial disease, as it would be possible to treat high-risk patients more aggressively” (Spec. 2).

*The Claims*

Claims 13–28 are on appeal. Claim 13 is representative and reads as follows:

13. A method of using a quantitative PCR (“QPCR”) machine to determine gene expression levels of certain bladder cancer progression markers in order to predict the likelihood of an individual’s bladder cancer progression, said method encompasses reducing sources of noise in said determination, comprising:

- a. Using QPCR to determine gene expression levels of certain harmful and protective markers from an individual with stage Ta or T1 bladder cancer wherein a Ct value for said markers indicates the number of amplification cycles until a signal threshold has been reached in inverse relationship to the expression level for said markers;
- b. Calculating a value for the expression levels of said protective markers by summing the Ct values of said protective markers and dividing by the number of said protective markers;

- c. Calculating a value for the expression levels of the said harmful markers by summing the Ct values of said harmful markers and dividing by the number of said harmful markers;
- d. Subtracting one of the calculated values obtained in steps b and c above from the other thereby obtaining a score based on reduced sources of noise in the Ct values; and
- e. If the score signifies increased expression levels of protective markers compared to expression levels of harmful markers it indicates a decreased risk of the individual's bladder cancer progression; or, if the score signifies increased expression levels of harmful markers compared to expression levels of protective markers it indicates an increased risk of the individual's bladder cancer progression.

*The Issues*<sup>2</sup>

- A. The Examiner rejected claims 13–28 under 35 U.S.C. § 101, as being directed to non-statutory subject matter (Ans. 2–9).
- B. The Examiner rejected claims 13–28 under 35 U.S.C. § 112, second paragraph, as indefinite (Ans. 9–10).
- C. The Examiner rejected claims 16, 20, and 26 under 35 U.S.C. § 112, first paragraph as failing to comply with the enablement requirement (Ans. 10–17).
- D. The Examiner rejected claims 13–15, 17–19, 21–25, 27, and 28 under 35 U.S.C. § 102(b) as anticipated by Glinskii<sup>3</sup> (Ans. 17–21).

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<sup>2</sup> The Examiner withdrew the provisional obviousness-type double patenting rejections (*see* Ans. 21).

<sup>3</sup> Glinskii, G., US 2009/0233279 A1, published Sept. 17, 2009 (“Glinskii”).

A. 35 U.S.C. § 101

The Examiner has rejected all of the claims on appeal under 35 U.S.C. § 101 as being directed to patent-ineligible subject matter. The Examiner finds that “claim(s) 13–28 are determined to be directed to a law of nature/natural principle” (Ans. 2). The Examiner reached this conclusion by applying the test set out in *Mayo Collaborative Services v. Prometheus Laboratories, Inc.*, 132 S. Ct. 1289 (2012), as directed in a 2012 guidance memo<sup>4</sup> (Ans. 2–9).

Appellants argue that the claims require the use of QPCR, which is an additional element that is significantly more than the natural principle of correlating protective or harmful gene expression levels with the likelihood of bladder cancer progression (App. Br. 12). Appellants also claim the “method of reducing noise is ‘significantly more than the natural principle itself’” (*id.*). Appellants also argue that the claims do not preempt the natural principle because “[n]o one is foreclosed from correlating gene expression with bladder cancer progression by other processes or means” (*id.* at 13). Finally, Appellants argue that the calculations recited in the claims are not conventional and routine steps because no reference has been cited that teaches these steps (*id.* at 14).

We agree with the Examiner that, under the two-step test of *Mayo*, the claims are not directed to patent-eligible subject matter. In *Mayo*, the Supreme Court applied its test to claims that are similar to those of the instant application and found them patent-ineligible under § 101.

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<sup>4</sup> 2012 Interim Procedure for Subject Matter Eligibility Analysis of Process Claims Involving Laws of Nature (July 3, 2012).

Specifically, the claimed invention at issue in *Mayo* was a “method of optimizing therapeutic efficacy for treatment of an immune-mediated gastrointestinal disorder” comprising administering a certain class of drug and then determining the level of 6-thioguanine (6-TG) in a patient, where a level of 6-TG below or above certain amounts indicated a need to increase or decrease, respectively, the drug dosage. *Mayo*, 122 S. Ct. at 1295.

Claim 13 of the instant application is similar, in that it is directed to a method of predicting whether a given patient’s bladder cancer is or is not likely to progress from an early, superficial stage to a muscle-invasive stage, by measuring the gene expression of particular harmful and protective markers and comparing the result to a control.

The *Mayo* Court concluded that the claims at issue in that case “set forth laws of nature—namely, relationships between concentrations of certain metabolites in the blood and the likelihood that a dosage of a thiopurine drug will prove ineffective or cause harm.” *Id.* at 1296.

Similarly here, claim 13 on appeal sets forth a law of nature—namely, a relationship between the level of expression of particular harmful and protective markers and the likelihood that a bladder cancer will progress to a more invasive form. Under the first step of the *Mayo* test claim 13 on appeal is directed to a law of nature or natural phenomenon.

The *Mayo* Court next turned to the question “[w]hat else is there in the claims before us?” *Id.* at 1297. The claims in *Mayo* included an ““administering”” step, a ““determining”” step, and a ““wherein”” clause. *Id.* The Court concluded that “[t]he upshot is that the three steps simply tell doctors to gather data from which they may draw an inference in light of the

correlations.” *Id.* at 1298. In other words, “the claims inform a relevant audience about certain laws of nature; any additional steps consist of well-understood, routine, conventional activity already engaged in by the scientific community; and those steps, when viewed as a whole, add nothing significant beyond the sum of their parts taken separately.” *Id.* The Court concluded that “the steps are not sufficient to transform unpatentable natural correlations into patentable applications of those regularities.” *Id.*

Like the steps of the claims in *Mayo*, the manipulative steps of claim 13 on appeal also “consist of well-understood, routine, conventional activity already engaged in by the scientific community.” *Id.* “Using QPCR” to measure the expression level of a given gene is conventional, as shown by Mack<sup>5</sup> and Glinskii: “Often, amplification-based assays are performed to measure the expression level of bladder cancer-associated sequences. . . . Methods of quantitative amplification are well known to those of skill in the art” (Mack ¶ 153); “Q-PCR reactions and measurements were performed . . . . The results were normalized to the relative amount of expression of an endogenous control gene GAPDH” (Glinskii ¶ 91). Our reviewing court has also recognized that the use of PCR was a “well-understood, routine, and conventional activity” that is insufficient to confer patent eligibility. *See Genetic Techs. Ltd. v. Merial L.L.C.*, 818 F.3d 1369, 1377 (Fed. Cir. 2016) (“[T]he physical steps of DNA amplification and analysis of the amplified DNA to provide a user with the sequence of the non-coding region do not, individually or in combination, provide sufficient inventive concept to render claim 1 patent eligible.”); *Ariosa Diagnostics, Inc. v. Sequenom, Inc.*,

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<sup>5</sup> Mack et al., US 2004/0076955 A1, published Apr. 22, 2004 (“Mack”).

788 F.3d 1371, 1377 (Fed. Cir. 2015) (“Using methods like PCR to amplify and detect cffDNA was well-understood, routine, and conventional activity in 1997.”).

The step of comparing gene expression levels is also routine, as also shown by Mack and Glinskii. Mack states that its “invention provides nucleic acid and protein sequences that are differentially expressed in bladder disease or cancer relative to normal tissues” (Mack ¶ 104). Glinskii teaches “[m]olecular signatures can then be identified from these sets of transcripts exhibiting concordant expression changes between metastatic tumor and stem cell samples” (Glinskii ¶ 60). The final step of claim 13 simply preserves and informs others of the correlation. *See Genetic Tech.*, 818 F.3d at 1379 (finding “instruction to undertake a simple comparison step does not represent an unconventional, inventive application sufficient to make the claim patent-eligible”).

Thus, when claim 13 is considered as an ordered combination, it informs a relevant audience of certain laws of nature: specifically, that the expression level of particular genes can be used to distinguish between bladder cancer patients whose cancer is more likely or less likely to progress. All of the additional steps of claim 13 consist of well-understood, routine, conventional activity already engaged in by the scientific community such as Mack or Glinskii.

We conclude that, under the *Mayo* test, claim 13 is directed to patent-ineligible subject matter. The rejection of claim 13 under 35 U.S.C. § 101 is affirmed. Independent claims 17 and 23 add more data manipulation steps, but those steps merely determine the accuracy of the levels of expression

relative to other (protective or harmful) markers, in order to determine the likelihood of bladder cancer progression. These claims also add nothing more than routine and conventional steps of data manipulation that are required to inform the relevant audience of the natural principle itself. We therefore conclude that all of the claims on appeal are directed to patent-ineligible subject matter.

*B. 35 U.S.C. § 112, second paragraph*

The Examiner finds “Claims 13, 17 and 23 recite ‘using’ QPCR but since the claims do not set forth any positive steps involved in the process of using, it is unclear what process applicant is intending to encompass by the term ‘using’” (Ans. 9).

Appellants contend:

The independent claims set forth a number of steps “in the process of using,” including: determining “gene expression levels of certain harmful and protective markers” [claims 13, 17 and 23]; “calculating a value for the expression levels of” harmful and protective markers [claims 13, 17 and 23]; “subtracting one of the calculated values” [claims 13, 17 and 23]; and “assigning weights to said markers according to the significance of each marker” [claims 17 and 23].

(App. Br. 14).

We find that Appellants have the better position. The Examiner has not pointed to evidence showing that those skilled in the relevant art would not understand what process is referred to as quantitative PCR (QPCR) and in fact argues, in the context of the § 101 rejection, that QPCR is “old, conventional, and routine in the art of differential gene expression determination” (Ans. 5). As already noted, Glinskii teaches “Q-PCR

reactions and measurements were performed with the SYBR-Green and ROX as a passive reference, using the ABI 7900 HT Sequence Detection System” (Glinskii ¶ 91). Thus, the evidence supports Appellants’ position that the ordinary artisan would understand the process steps involved in “using QPCR.” We reverse this rejection.

*C. 35 U.S.C. § 112, first paragraph, enablement*

The Examiner finds “the combination of the breadth of the claims which encompass a four-gene signature in combination with the limitation that one of the four genes must be MBNL2 as a ‘protective marker’ is unpredictable” (Ans. 12). The Examiner finds that the prior art references “teach that the MBNL2 gene marker is considered to be a harmful marker rather than a protective marker as currently claimed and that the MBNL2 gene marker would be predictive of poor prognosis” (*id.*). The Examiner finds there is no working example and “[c]onflicting information regarding the status of the MBNL2 marker as being a ‘protective’ marker *versus* a ‘harmful’ marker associated with progression or death from bladder cancer is found in the specification” (*id.* at 15). The Examiner concludes “it would require undue experimentation to practice the invention as presently claimed” (*id.* at 17).

Appellants contend “Table 4 of Application Serial Nos. 13/316733 and 13/316765 (see **Evidence Appendix**) shows . . . the correlation with progression/non-progression events for both MBNL2 levels expression levels was statistically significant” (App. Br. 15). Appellants contend, regarding the cited art, that the results “do not indicate anything about

whether MBNL2 is or is not a progression marker for *bladder cancer*” (App. Br. 17).

We find that Appellants have the better position. The data from the Evidence App’x regarding MBNL2 and FABP4 is reproduced, in part, below:

24 MONTHS							
Marker	Type (P or H)*	T Test	Wilcoxon signed- rank test	KS Test	Cox Regression Analysis		ROC
		<i>P-value</i>	<i>P-value</i>	<i>P-value</i>	<i>Beta Coefficient</i>	<i>P-value</i>	<i>AUC</i>
<b>MBNL2</b>	P	0.000	0.000	0.000	0.676	0.000	0.757
<b>FABP4</b>	P	0.001	0.001	0.023	0.195	0.001	0.703

“Table 4 – Markers selected for their correlation with clinical determination of bladder cancer progression or non-progression” (*see* App. Br. 28) (emphasis omitted).

The Specification teaches “for each group of patients weight the preferred protective markers, for example MBNL2 and/or FABP4; and weight the preferred harmful markers, for example UBE2C” (Spec. 11).

Mack lists the protein identified by the Examiner as MBNL2 in a list of “Genes predictive of bladder cancer progression” (Mack 133), Clarke<sup>6</sup> lists MBLL39 in a table titled “Up Regulated in UPTG versus UPNTG” (Clarke 12), while Bignotti<sup>7</sup> lists MBNL2 in a table titled “Up-regulated genes expressed at least 2-fold higher in metastasis vs primary OSPC

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<sup>6</sup> Clarke et al., US 2006/0019256 A1, published Jan. 26, 2006 (“Clarke”).

<sup>7</sup> Bignotti et al., *Gene expression profile of ovarian serous papillary carcinomas: identification of metastasis-associated genes*, 196 Am. J. Obstet. Gynecol. 245.e1-245.e11 (2007) (“Bignotti”).

[ovarian serous carcinomas]” (Bignotti 245.e5). Sánchez-Carbayo<sup>8</sup> teaches issues relevant to microarray analyses (*see* Sánchez-Carbayo 29, col. 2).

As we balance the *Wands*<sup>9</sup> factors evidence, we find that the evidence supporting enablement of MBNL2 and FABP4 as progression markers including the disclosure in the evidence appendix and Specification outweighs both the unclear teachings in Mack and Clarke regarding MBNL2 and bladder cancer progression as well as the unrelated teachings of Bignotti drawn to ovarian cancer and the general concerns of Sánchez-Carbayo. We note the narrow nature of claims 16, 20, and 26, limited to analysis of particular genes as protective and harmful for bladder cancer, as well as the acknowledged high level of skill in the art (*see* Ans. 16). We conclude that the evidence of record does not support a finding that undue experimentation would have been required to use the invention.

*D. 35 U.S.C. § 102(b) over Glinskii*

The Examiner finds Glinskii teaches “a method comprising: (a) determining gene expression levels of certain harmful and protective markers from an individual with early stage bladder cancer” (Ans. 18). The Examiner finds:

Glinskii report that in paragraph 0072 that “[s]imilar types of methods (e.g., Kaplan-Meier methods) can also be used to determine a signature’s prediction capabilities of a short relapse survival after therapy in patients with an early stage disease”. Therefore, Glinskii teaches (c) calculating a value for the

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<sup>8</sup> Sánchez-Carbayo, M., *Use of High-Throughput DNA Microarrays to Identify Biomarkers for Bladder Cancer*, 49 *Clinical Chemistry* 23–31 (2003) (“Sánchez-Carbayo”).

<sup>9</sup> *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 2008).

expression levels of the said protective markers, (d) calculating a value for the expression levels of the said harmful markers, and especially per claim section (e), subtracting one of the calculated values obtained in steps (c) and (d) above from the other thereby obtaining a score.

(Ans. 20).

Appellants contend:

The claims also all require “subtracting” one of these sums of Ct values (*i.e.*, either the sum corresponding to harmful marker gene expression level or the sum corresponding to protective marker gene expression level) from the other, “thereby obtaining a score based on reduced sources of noise in the Ct values.” This step is also not disclosed in Glinskii

(App. Br. 18).

We find that Appellants have the better position. Although Glinskii teaches the use of QPCR (Glinskii ¶ 91) for predicting clinical outcomes of diseases including bladder cancer (Glinskii, claims 10, 14) using expression profile data (Glinskii ¶ 38), the Examiner does not identify a teaching in Glinskii for a “subtracting” step where the summed values of protective markers is subtracted from the summed value of harmful markers as required by claims 13, 17, and 23. We have reviewed paragraphs 71, 72, and 87 of Glinskii, identified by the Examiner (*see* Ans. 33–34), and find no specific teaching that either the “Kaplan-Meier methods” or “weighted survival score analysis” and normalization of the gene expression values necessarily involved any subtraction of protective marker values from harmful marker values as required by the claims. We reverse this rejection.

SUMMARY

In summary, we affirm the rejection of claims 13–28 under 35 U.S.C. § 101, as being directed to non-statutory subject matter.

We reverse the rejection of claims 13–28 under 35 U.S.C. § 112, second paragraph, as indefinite.

We reverse the rejection of claims 16, 20, and 26 under 35 U.S.C. § 112, first paragraph as failing to comply with the enablement requirement.

We reverse the rejection of claims 13–15, 17–19, 21–25, 27, and 28 under 35 U.S.C. § 102(b) as anticipated by Glinskii.

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a).

AFFIRMED